DOI:
10.1097/j.pain.0000000000001491

Document Version
Peer reviewed version

Title page

Chronic Pain is Associated with Worse Predicted Brain Age in Community-Dwelling Older Individuals

Y. Cruz-Almeida, MSPH, PhD[1-5]*, R.B. Fillingim, PhD[1,2], J.L. Riley III, PhD[1,2], A.J. Woods, PhD[3-6], E. Porges, PhD[3-6], R. Cohen, PhD[3-6], J. Cole, PhD[7]

[1]Pain Research & Intervention Center of Excellence, University of Florida, Gainesville, Florida.

[2]Institute on Aging, University of Florida, Gainesville, Florida.

[3]Cognitive Aging & Memory Clinical Translational Program, McKnight Brain Foundation, University of Florida, Gainesville, Florida.

[4]Department of Aging & Geriatric Research, College of Medicine, University of Florida, Gainesville, Florida.

[5]Department of Neuroscience, College of Medicine, University of Florida, Gainesville, Florida.

[6]Department of Clinical & Health Psychology, College of Health Professions, University of Florida, Gainesville, Florida.

[7]Department of Neuroimaging, Institute of Psychiatry, Psychology & Neuroscience, King's College London. Centre for Neuroimaging Sciences, De Crespigny Park, London, UK, SE5 8AF.

Corresponding author: Yenisel Cruz-Almeida, MSPH, PhD

Corresponding author's address: PO BOX 112610, Gainesville, FL 326010

Corresponding author's phone and fax: 352-294-5845, 352-294-

Corresponding author's e-mail address: cryeni@ufl.edu

Running head: (limit 50 characters) Pain and Brain Aging

Number of words in abstract: (limit 250 words)

Number of words in main text: (limit 4,500 words), currently 4,601 (though see note on cutting bits of the Discussion).

Introduction (limit 500 words): 499

Discussion (limit 1500 words): 1,527

Number of figures: 9

Number of tables: 3

Conflict of Interest: Yenisel Cruz-Almeida, Joseph L. Riley, XXX, James Cole report no conflict of interest.

Acknowledgements: This work was supported by the National Institutes of Aging (K01AG048259 to YCA), the Cognitive Aging & Memory Clinical Translational Program, McKnight Brain Foundation, the University of Florida Claude D. Pepper Older Americans Independence Center (P30AG028740 to YCA). James Cole was supported by the UK Research and Innovation Fellowship (reference # MR/R024790/1).

ABSTRACT

Limit 250 words

Objective: To determine the associations between chronic pain and apparent "brain-age" using neuroimaging in community-dwelling individuals 60 to 83 years old.

Methods: The NEPAL study included community-dwelling older individuals (n=47) who completed demographic, psychological, and clinical pain assessments followed by a somatosensory function battery and a T1-weighted MRI. We estimated a brain-predicted age difference (brain-PAD; calculated as brain-predicted age minus chronological age), using an established machine-learning model. ANCOVAs and Pearson/Spearman correlations were used to determine associations of brain-PAD with pain, somatosensory and psychological function.

Results: Individuals with chronic pain (n=33) had "older" appearing brains compared to those without (n=14, $F(1,41)=4.9$, $p=0.033$). Greater average worst pain intensity was associated with an "older" brain ($r=0.464$, $p=0.011$). Among participants with chronic pain, those that reported having pain treatments during the past 3 months had "younger" appearing brains compared to those that did not ($F(1,27)=12.3$, $p=0.002$). An "older" brain was significantly associated with decreased vibratory ($r=0.323$, $p=0.033$) and thermal ($r=0.345$, $p=0.023$) detection, deficient endogenous pain inhibition ($F(1,25)=4.6$, $p=0.044$), lower positive affect ($r=-0.474$, $p=0.005$), having a less agreeable personality ($r=-0.439$, $p=0.020$), and being less emotionally stable or having a more neurotic personality ($r=-0.387$, $p=0.042$).

Interpretation: Our findings suggests that chronic pain has a negative impact on brain structure during aging, even in otherwise healthy, community-dwelling older individuals. Importantly, our results suggest that pain is causing added "age-like" brain atrophy. Potentially, using a brain aging biomarker in people with chronic pain could help identify people at greater risk of functional decline and poorer health outcomes.

INTRODUCTION

Over 1.5 billion people worldwide suffer from chronic pain and more Americans are affected by chronic pain than by diabetes, heart disease and cancer combined (IOM report, 2011). In particular, epidemiological evidence suggests an age-related increase in pain prevalence with back and knee pain the most commonly reported in those over 65 years of age (Patel et al., 2013). Chronic pain in older individuals is a growing public health problem; effective treatments are lacking and pain detrimentally impacts physical and cognitive function, ultimately decreasing quality of life and well-being.

Pain is associated with both direct (i.e., the experience of pain) and indirect effects on the brain. Neuroimaging studies have established the prominent role of the brain in pain perception and modulation (Apkarian et al., 2012) and in the integration of sensory, motor, emotional and cognitive components that give rise to the complex, individualized pain experience. While most chronic pain conditions are associated with changes to brain structure and function, these structures are equally impacted by normal as well as pathological aging processes. Indeed, chronological aging has been associated with both global and spatially-localized changes to brain structure and function which may be very similar to brain changes reported in chronic pain states. Accelerated brain aging has been reported in individuals with fibromyalgia (Kuchinad et al., 2007), temporomandibular disorders (Moayedi et al., 2012) and low back pain (Apkarian et al., 2004). However, these studies have compared younger, middle-age and older individuals to determine global differences in gray matter not attributed to aging alone. In addition, several preliminary investigations in older adults with and without low back pain (n=8/group) suggest that chronic pain negatively impacts the brain above and beyond age-related effects (Buckalew et al., 2008; 2010; 2013).

Recently, multivariate methods have been developed to define statistical models of healthy brain aging. Using machine-learning analysis of neuroimaging data, chronological age can be accurately predicted in healthy individuals (Franke et al., 2010). Using this model, added ageing effects have been reported in Alzheimer's disease, mild cognitive impairment, epilepsy and after traumatic brain injury. Meanwhile, protective factors, such as years of education, physical exercise and practicing meditation, have been associated with a positive influence on brain ageing (Cole & Franke, 2017). Furthermore, recent work found that having an older-appearing brain was associated with weaker grip strength, poorer lung function, slower walking speed, lower fluid intelligence, higher allostatic load and increased overall mortality risk (Cole et al., 2018).

Here, we employed a neuroimaging-derived biomarker of the brain aging process to investigate how chronic pain affects brain aging in n=47 community-dwelling individuals aged 60 to 83, n=33 of whom reported chronic pain. Consistent with previous work (Cole et al., 2018), we estimated a brain-predicted age difference (brain-PAD; calculated as brain-predicted age minus chronological age) using structural neuroimaging (T1-weighted magnetic resonance imaging (MRI)), processed through an established analysis pipeline. This included comparing voxelwise gray and white matter volume images to a statistical model that accurately predicts chronological age from neuroimaging data in healthy people; trained on n=2646 independent healthy adults aged 18-90 years. We hypothesized that 1) Older adults with chronic pain will have a greater brain-PAD compared to older adults that did not report chronic pain during the past three months; and 2) a greater brain-PAD will be associated with worse pain, somatosensory and psychological function.

SUBJECTS/MATERIALS AND METHODS

Participants

Community-dwelling individuals over the age of 60 who were native English speakers were recruited as part of an ongoing project at the University of Florida (UF) studying the neurobiology of age-related differences in pain modulation and its impact on function (Neuromodulatory Examination of Pain and Mobility Across the Lifespan [**NEPAL**]). Potential participants were screened over the phone and again in person. Exclusionary criteria included: 1) Alzheimer's, Parkinson's or other condition directly impacting the brain; 2) serious psychiatric conditions (e.g., schizophrenia, major depression, bipolar disorder), 3) uncontrolled hypertension (blood pressure >150/95 mm Hg), heart failure, or history of acute myocardial infarction; 4) systemic rheumatic disorders (i.e., rheumatoid arthritis, systemic lupus erythematosus, fibromyalgia); 5) chronic opioid use; 6) magnetic resonance imaging (MRI) contraindications; 7) excessive anxiety regarding protocol procedures; 8) hospitalization within the preceding year for psychiatric illness; 9) HIV or AIDS; and 10) cognitive impairment (Modified Mini-Mental State Examination (3MS) score < or = 77, Teng et al., 1987). Participants were recruited through posted fliers, newspaper ads, and word of mouth referrals. As the NEPAL study aims to recruit older individuals with and without chronic pain representative of the aging population, individuals were not specifically recruited for a specific pain condition. All procedures were reviewed and approved by the University of Florida's Institutional Review Board and all participants provided verbal and written informed consent. Participants attended three separate laboratory visits: 1) a health assessment session (i.e., demographic, general health, pain, and psychological information), 2) a quantitative sensory testing session, and 3) a neuroimaging session detailed below.

Health Assessment Session

Upon verbal and written informed consent, participants completed questionnaires, which included general health and demographic information including all medications taken. Similar to our previous studies in older individuals (Cruz-Almeida et al., 2013), a trained research coordinator assessed prior and current health and pain history, including detailed information regarding smoking, drinking and exercise habits. The following instruments were also administered during this session to assess self-reported pain and psychological function:

A) Self-reported Pain: Pain groups were determined using a combination of pain presence (*Have you had pain during the past 3 months?*) and reported difficulty in performing activities on a daily basis (*Pain during walking*,

using stairs, in bed, sitting or lying, and standing). Participants were categorized to the chronic pain group if they reported pain during the past 3 months and also reported any degree of difficulty due to pain in performing activities on a daily basis. This is consistent with the Task Force for the Classification of Chronic Pain consensus for the 11th version of the International Classification of Diseases (ICD-11) of the World Health Organization (WHO) (Treede et al., 2015). Participants also completed a standardized pain history interview regarding the presence of pain across several body regions (i.e., head/face, neck, shoulders, arms, hands, chest, stomach, upper and lower back, leg, knees, and feet) using a validated body manikin (Cruz-Almeida et al., 2005; Margolis et al., 1988). Participants were asked to choose the location of their worst pain and asked about its duration, frequency during the past week, intensity on average, and how hard it was to deal with their worst pain. Participants were also asked if they received any treatments or tried any self-remedies (something they may have done at home) to relieve their worst pain during the past 3 months (Yes/No). Finally, all participants were queried regarding current medications along with indication and percent pain relief obtained from these.

B) **Psychological and Emotional Function:** The 20-item **Center for Epidemiologic Studies Depression Scale (CES-D)** questionnaire was used to measure the frequency of depressive symptoms during the past week on a 4-point Likert scale (Radloff, 1977). The Positive and Negative Affect Scale (PANAS) was also administered consisting of 20 items rated on a 5-point scale (Watson et al., 1988; Crawford et al., 2004). We asked the participants to report how they generally feel with high scores on positive affect reflecting enthusiasm, energy, and alertness, while higher scores on negative affect reflect distress and aversive mood states. **The Ten Item Personality Measure (TIPI)** is a brief 10-item measure of the Big Five (or Five-Factor Model) personality dimensions: Extraversion (E), Agreeableness (A), Conscientiousness (C), Emotional Stability (ES) and Openness to Experience (O). Each dimension is measured by two descriptors, one of each pair is reverse-scored. Participants rate themselves on a 7-point scale ranging from 1-disagree strongly to 7- agree strongly. The TIPI was created to be finished within a minute (Gosling et al., 2003).

Quantitative Sensory Testing (QST) Session

QST was used to assess the functional properties of peripheral receptor and somatosensory pathways, similar to the methodology previously reported by our group in older individuals (Cruz-Almeida et a., 2013). All QST procedures were performed in a quiet room with an approximate temperature between 21°C and 23°C. All subjects were seated in a

comfortable chair with armrests and a semi-reclining back. Standardized testing was performed at the thenar eminence and on the first metatarsal head on all participants. An overview of the testing procedures was explained to the subject and for each different modality, specific instructions were also explained immediately before beginning the test. Measurement of a particular type of threshold was first demonstrated, and at least one practice trial was conducted to ensure that subjects understood the testing procedures. Vibratory and thermal detection and pain threshold measurements were obtained with the TSA-II Neurosensory Analyzer and accompanying software (Medoc Ltd., Ramat Yishai, Israel). The method of limits was used to obtain all detection thresholds.

A) Vibration: The handheld VSA-3000 circular probe (contact tip=1.22 cm^2) of the Medoc system was used to measure vibratory thresholds for a 100 Hz stimulus frequency. Subjects were asked to indicate as soon as they felt the vibratory sensation. Three trials, separated by ~10 sec each, began at 0 μm at a rate of 0.5 μm/sec and increased until the subject indicated that the stimulus was felt or until the maximum amplitude of 130 μm was reached. The mean value across the three trials was calculated as the vibratory detection threshold for each site.

B) Thermal Detection: A 30 x 30 mm thermode connected to the TSA-II Neurosensory Analyzer was used to deliver thermal stimuli. Each trial began at 32°C and the temperature decreased (for cool) or increased (for warm) at a rate of 1°C/sec until the subject perceived the stimulus or until the stimulus reached the cutoff value (0°C for cool and 50°C for warm). Each trial was separated by ~10 sec. The average of threshold temperatures across four trials was calculated as detection threshold for each modality and test site.

C) Thermal Pain: Subjects were instructed to indicate as soon as the sensation changed from "just being cold to being painfully cold" or from "just being hot to being painfully hot." Each trial began at 32°C and was either decreased (for cold pain) or increased (for heat pain) at a rate of 1.5°C/sec until pain threshold was reached or the cutoff value was reached (0°C for cold pain and 50°C for heat pain). Each trial was separated by at least 20 sec. The mean across three trials at each test site was calculated as the pain detection threshold.

D) Conditioned Pain Modulation Procedure: A subset of participants completed a conditioned pain modulation (CPM) paradigm as recommended by Yarnitsky and colleagues (2015). Heat stimulus was given at an ascending intensity and was discontinued by the subject at pain-40 (pain level of 40/100). A cold-water immersion of 1 minute was used as the 'conditioning' stimulus. The latter was reported by most participants as mild to moderately

painful. The 'conditioned' test stimulus was presented immediately after the conditioning stimulus, providing a 'cleaner' representation of pain modulation, free of biases such as distraction. A percent change in pain inhibition was calculated as a first minus last temperature divided by first temperature (X 100) calculation whereby inhibition was denoted by a negative value, and pain facilitation by a positive value as recommended by expert consensus (Yarnitsky et al., 2015).

Neuroimaging Session

MRI data were collected at the University of Florida's McKnight Brain Institute on the Advanced Magnetic Resonance Imaging and Spectroscopy (AMRIS) facility's Philips (Best, the Netherlands) 3-Tesla scanner using a 32-channel radio-frequency coil. A high resolution, T1-weighted turbo field echo anatomical scan was collected using the following parameters: TR = 7.2 ms, TE = 3.3 ms, 170 slices acquired in a sagittal orientation, flip angle = 8 degrees, 1 mm^3 resolution. Head movement was minimized via cushions positioned inside the head coil and instructions to participants.

Brain-predicted age biomarker

The brain aging biomarker used here was derived using the established 'brain-age' framework (Cole & Franke, 2017). This involved training a machine-learning model to accurately predict chronological age from neuroimaging data in 2,646 healthy individuals (age mean = 41.17 ± 19.69 years; age range = 18 – 90 years; males = 1,333; females = 1,313). This used segmented and spatially-normalized T1-weighted MRI scans as the predictor variables in a Gaussian Processes regression, with chronological age as the outcome variable. As per previous reports (Cole et al., 2017), model accuracy was high (assessed using ten-fold cross-validation), with a mean absolute error of 4.9 years and a correlation between chronological age and 'brain-predicted' age of r = 0.95. Then, using the regression model trained on the full independent dataset (n=2646), brain-predicted age values were generated for the n=47 participants in the current study. The individual participants' chronological age was then subtracted from this brain-predicted age value to generate a brain-predicted age difference (brain-PAD) score, which was used for further analysis. Imaging data comprising the training dataset were obtained via publicly-available repositories (Supplementary Table 1) and were screened according to local study protocols to ensure that they were free of neurological and psychiatric disorders, had no history of head trauma and other major medical conditions. Ethical approval for each initial study and subsequent data sharing was verified for each data repository.

Experimental Design and Statistical Analysis

Data were entered by one experimenter and checked for accuracy by a different experimenter. QST data were z-transformed for each modality at each test site and then combined for analysis due to the multicollinearity within thermal and pain modalities. Thus, three standardized Z-scores were created for vibratory detection, thermal detection, and thermal pain thresholds and used for further statistical analysis. The combination of these modalities is appropriate based on the physiological properties of sensory channels (Willis & Coggeshall, 2004).

We used t-tests to compare groups with respect to continuous/discrete ordinal variables and $\chi 2$ analyses to assess associations with nominal variables. Assumptions underlying each statistical test were tested. Two-way analysis of covariance (ANCOVA) procedures were conducted with Pain Group and Sex as between subject factors controlling for chronological age and exercise. Sex was entered as a between-subjects factor because of previously reported sex-differences in predicted brain age (Cole et al., 2018) as well as sex-based differences in brain alterations across chronic pain conditions (Gupta et al., 2017). Chronological age was entered as a covariate due to the wide age range of our sample (60-83) and the known non-linear brain changes that occur in old age (ref). Finally, there were significant differences between groups regarding regularly exercising, hence the variable "exercise" was also included as a covariate in all analysis. We employed Pearson correlations for interval level variables while Spearman correlations were used for ordinal level variables to assess associations between Brain-PAD with pain, somatosensory and psychological variables. Partial correlations were also used accounting for sex, chronological age, and exercise. A probability less than 0.05 was considered statistically significant, and no global corrections for multiple comparisons were performed given the exploratory nature of our study. Data analyses were performed using IBM SPSS 25 software.

RESULTS

Forty-seven older adults ranging in ages from 60 to 83 years of age (mean age = 70.9 ± 6.0, 74.5% female) participated in our study. The majority of our sample (n = 33, 70%) reported chronic pain and 63% reported pain at multiple sites (40% reported pain at 2 different locations). Sample clinical and demographic characteristics are presented in Table 1. There were no significant differences between the groups in relation to self-reported health and lifestyle characteristics between the groups except with respect to exercise (Table 2). Detailed pain distribution is presented in Table 3.

Brain-PAD and Presence of Pain

A two-way ANCOVA was used to compare brain-PAD between pain groups and sex, controlling for chronological age and exercise. Levene's test and Shapiro-Wilks normality checks were carried out and the assumptions met. There was a significant difference in brain-PAD between older adults who reported chronic pain (1.5 ± 1.6) versus those that did not (-4.0 ± 1.9, $F(1,41) = 4.9$, $p = 0.033$, ANCOVA, see Figure 3). There was no significant sex difference in brain-PAD ($F(1,41) = 3.8$, $p = 0.057$, ANCOVA) or Pain Group X Sex interaction ($F(1,41) = 1.8$, $p = 0.187$, ANCOVA).

Brain-PAD and Worst Pain Characteristics

Worst pain location within the participants that experienced musculoskeletal pain (n = 33) is depicted in Figure 2. Brain-PAD was strongly correlated with average intensity of the worst pain ($r = 0.464$, $p = 0.011$). However, self-reported worst pain duration ($r = -0.100$, $p = 0.606$) and worst pain frequency during the past week ($r = 0.039$, $p = 0.842$) were not significantly correlated with brain-PAD. Adjusted partial correlations controlling for sex, chronological age, and exercise did not significantly change our results. We compared brain-PAD between individuals reporting receiving treatments (including self-remedies at home) to relieve their worst pain during the past 3 months using a two-way ANCOVA (Between-subject factors: pain groups and sex, controlling for chronological age and exercise). Levene's test and Shapiro-Wilks normality checks were carried out and the assumptions met. There was a significant difference in Brain-PAD between individuals who reported receiving treatments to relieve their worst pain (-3.9 ± 1.5) versus those that did not (5.6 ± 1.4, $F(1,27) = 12.3$, $p = 0.002$, ANCOVA, Figure 4). As part of our detailed pain interview, we also asked participants the percent pain relief they experienced from their pain medications and similarly, there was a strong association between greater pain relief from medications with brain-PAD (Pearson's $r = -0.423$) that was not statistically significant ($p=0.091$, $n = 16$, Figure 5).

Brain-PAD and Psychological Function

Spearman correlations were used to determine associations between brain-PAD and psychological variables. There were no significant associations between brain-PAD and the psychological variables across all participants (p's > 0.05). However, among individuals reporting chronic pain (n = 33), brain-PAD was significantly associated with PANAS-Positive Affect Trait (r = -0.474, p = 0.005), TIPI-Agreeableness (r = -0.439, p = 0.020), TIPI-Emotional Stability (r = -0.387, p = 0.042, Figure 6). Brain-PAD was not correlated with CES-D (r = 0.122, p = 0.414), PANAS-Negative Affect (r = 0.033, p = 0.857), TIPI-Extraversion (r = -0.135, p = 0.494), TIPI-Conscientiousness (r = -0.301, p = 0.120) or TIPI-Openness to Experiences (r = 0.119 p = 0.819).

Brain-PAD and QST

Pearson's Moment correlations were used to determine associations between brain-PAD and QST variables. Greater vibratory detection thresholds were significantly associated with greater Brain-PAD (i.e., older brain) (r = 0.323, p = 0.033, Figure 7a). Similarly, greater thermal detection thresholds were also significantly associated with greater Brain-PAD (i.e., older brain) (r = 0.345, p = 0.023, Figure 7b). There were no associations between Brain-PAD and thermal (r =0.057, p = 0.719) or pressure pain thresholds (r = 0.230, p = 0.137). Subgroup analysis within persons with pain did not significantly change our results.

Brain-PAD and CPM

Across the subset of all participants who underwent the CPM procedure (n = 41), there were no strong correlations between brain-PAD and CPM scores (Pearson's r = 0.132, p = 0.409). However, among a subset of individuals reporting chronic pain (n=27), brain-PAD was correlated with CPM scores (Pearson's r = 0.346, Figure 8), but this coefficient was not statistically significant (p = 0.077). Finally, we wanted to explore whether there was a difference in CPM depending on a participant's brain-PAD. Individuals with a lower brain-PAD exhibited significantly greater endogenous pain inhibition during the CPM procedure (-0.06 ± 0.01) compared to those that had a greater brain-PAD (0.01 ± 0.02, F (1,25) = 4.6, p = 0.044, ANCOVA, Figure 9). Adding sex to the model, decreased the statistical significance of this finding (p = 0.074).

DISCUSSION

Here, we conducted the first examination of how chronic pain influences a biomarker of brain ageing in community-dwelling older adults. Several important contributions emerged from this investigation. First, older individuals with chronic pain had an "older" appearing brain compared to those without chronic pain and greater average pain intensity was associated with an "older" brain. Second, among participants that experienced chronic pain, those that reported having pain treatments during the past 3 months had a "younger" appearing brain compared to those that did not report receiving any pain treatments. Finally, an "older" brain was significantly associated with decreased somatosensory perception, deficient endogenous pain inhibition, lower positive affect, having a less agreeable personality, and being less emotionally stable (or having a more neurotic personality).

As hypothesized, chronic pain was associated with an "older" brain relative to an individual's chronological age. Older pain-free controls had on average a brain that looked 4 years younger than their chronological age while the chronic pain group had on average a brain that appeared 2 years older than their chronological age adjusting for important covariates. In a previous study, each extra year of brain-predicted age (i.e., having a brain-PAD score of +1) resulted in a 6.1% relative subsequent increase in the risk of death between ages 73 and 80 (Cole et al., 2018). This raises the possibility that chronic pain could increase the risk of mortality, though long-term follow-up will be necessary to probably test this.

Our findings are consistent with previous chronic pain research, that used univariate methods to infer that pain is associated with accelerated brain aging; in individuals 25 to 65 years of age with fibromyalgia (Kuchinad et al., 2007) and 15 to 55 years of age in temporomandibular disorders (Moayedi et al., 2012). Apkarian and colleagues (2004) also reported global decreases in gray matter in people with chronic low back pain that were significantly greater than the expected age-related decreases alone. While their sample were aged 20-75 years of age, only 5 participants could be considered older individuals (60 to 75 years of age). Thus, the inclusion of younger and middle-aged individuals in these previous studies has hindered the direct examination of pain's impact on the aging brain, given the known age-related decrements in the brain's gray and white matter. However, our findings directly support several previous preliminary investigations in older adults with low back pain (n=8/group) where pain was significantly associated with significant changes in gray and white matter (Buckalew et al., 2008; 2010; 2013).

The variability in brain-predicted age in people with chronic pain was related to some characteristics of their pain experience. An older-appearing brain was associated with greater average intensity of a participant's worst pain, even after accounting for other potential confounders. In addition, individuals reporting they tried or received any pain-relieving treatments during the past 3 months had younger-appearing brains compared to those that did not. This is further supported experimentally, where those participants with "older" brains exhibited deficient endogenous pain modulation using a CPM paradigm. In combination, our findings suggest that chronic pain, when not sufficiently relieved, may negatively impact brain structure above and beyond the impact of chronological aging alone. Previously, Rodriguez-Raecke and colleagues (2009) reported gray matter decreases that were reversed when pain was successfully treated in middle-aged and older individuals. This is further supported by our observed association between pain relief and brain-predicted age, though this was not statistically significantly, potentially because of the small sample size (n = 16). Future prospective studies including pain interventions should address these questions with greater statistical power.

Better vibratory and thermal detection at two different body sites (i.e., hand and foot) was also associated with a younger brain. Aging is associated with a progressive decrease in vibratory and thermal perception (Lin et al., 2005; Guergova & Dufour, 2011). The main underlying causes appear to be skin aging and subsequent reductions in receptor density and superficial skin blood flow (Joynt, 2000). However, animal and human studies also suggest that changes relating to fiber loss and decreased conduction velocity, may also be involved (other refs, Guergova & Dufour, 2011). Interestingly, our results suggest that chronic pain may also be associated with accelerated peripheral nervous system aging with even subclinical decrements in somatosensation potentially impacting the brain and vice-versa. Although both vibratory and thermal systems have different components (e.g., sensory receptors, spinal cord pathways, thalamic termination sites) they still require the brain for integration and ultimately perception. Potentially, pain's impact on the peripheral nervous system may contribute to its negative impact on the brain, though mechanistic studies are needed to determine contributions across different individuals including the elderly.

Brain-PAD was also associated with positive, but not negative affect in those participants with chronic pain. Although the association between pain and negative affect is well-documented (Janssen, 2002; Wiech & Tracey, 2009), emerging evidence suggests that positive affect may independently mitigate pain in healthy and clinical populations (Zautra et al., 2005; Finan et al., 2013, Cruz-Almeida et al., 2013). This is consistent with the idea that positive and negative affect may have unique roles in modulating the pain experience (Finan & Garland, 2015). Although not currently understood, it is likely that positive affect impacts the pain experience via multiple converging supraspinal mechanisms. First, increased positive expectations in general may translate into positive expectations for recovery and potential treatment success (George & Robinson, 2010). Indeed, positive affect may therefore also enhance motivation and treatment adherence (Wiech & Tracey, 2013), which are important predictors of the success of exposure treatments (Ek et al., 2009). In addition, there is evidence that positive affect enhances extinction learning or inhibitory learning processes (Zbozinek & Craske, 2017), which may further optimize the efficacy of existing treatments.

Similarly, reporting a greater emotionally stable (or lower neuroticism) and an agreeable personality was associated with a younger appearing brain in those with chronic pain. In the Baltimore Longitudinal Study of Aging, larger orbitofrontal and dorsolateral prefrontal cortices and rolandic operculum were associated with a greater emotionally stability and lower Neuroticism personality type, and a larger orbitofrontal cortex with higher Agreeableness (Kapogiannis et al., 2013). The orbitofrontal cortex seems to be concerned with the evaluation of appetitive stimuli as well as aversive stimuli including pain (Plassmann et al., 2010; Morrison and Salzman, 2011). In addition, emotional stability/neuroticism is associated with depression/anxiety symptom severity and clinical and population-based studies have identified neuroticism as an important vulnerability factor for major depressive disorder (Boyce et al., 1991; Fanous et al., 2007; Hettema et al., 2006; Hirschfeld et al., 1989; Kendler et al., 2006; Kendler et al., 2004; Ormel et al., 2004). In turn, agreeableness was a significant positive predictor of attendance to a physical rehabilitation program after surgery (Hilliard et al., 2014). In general, distinct personality traits are associated with stable individual differences in gray matter volumes (Riccelli et al., 2017). Taken together, our findings underscore the idea that higher order traits such as general emotional valence and personality characteristics are a feature of large-scale brain structure and function that is negatively impacted by pain and sensitive to a brain aging biomarker.

Our study has some strengths and weaknesses. While the sample size for the training set was large, the NEPAL study cohort was smaller. However, NEPAL participants are well-characterized in multiple aspects relevant to the study of pain and aging within the biopsychosocial model of pain (Gatchel et al., 2002). In addition, our groups were very similar regarding age-related health comorbidities and overall medication intake. Second, the current analysis was cross-sectional; therefore, we cannot determine whether a specific brain-predicted age preceded or was subsequent to pain. Future studies are needed using longitudinal data to determine trajectories of brain ageing and how they relate to pain and future health outcomes. Third, the NEPAL participants were high functioning community-dwelling older individuals, who were relatively healthy for their age. They were cognitively normal, free from overt disability and neurological disorders. Given that greater self-reported exercise was associated with positive brain ageing in a previous investigation, it is possible that the true association between pain and brain-PAD was underestimated in our sample since everyone reported regularly exercising in our control group. Finally, our brain aging measure does not provide the anatomical specificity to determine which brain regions are specifically impacted since brain aging and pain do not uniformly impact the brain. Future studies including participants with more severe pain and lower levels of physical function are required to confirm and further elucidate these associations. In addition, the development of region-specific aging biomarkers will help the field and ultimately clinical practice.

Here, we present evidence that a clinically-relevant neuroimaging ageing biomarker previously associated with greater risk of general functional decline and mortality during ageing, is similarly sensitive to the presence and severity of the complex experience of pain in older individuals. Brain-PAD could be an intuitive general marker of brain health and has the potential to be estimated in large numbers of people, as structural MRI is collected routinely in clinical settings. Our findings also suggest that both pain treatments and psychological traits may significantly mitigate the effect of pain on the aging brain and could further decrease the risk of age-related deterioration and death.

REFERENCES

(limit to 40)

Cole, J. H., & Franke, K. (2017). Predicting Age Using Neuroimaging: Innovative Brain Ageing Biomarkers. Trends Neurosci, 40(12), 681-690.

TABLES

Table 1. Differences in demographic and clinical characteristics between the groups.

	No Chronic Pain (n=14)	**Chronic Pain (n=33)**	**p-value**
Chronological Age, mean ± SD years	71.5 ± 7.3	70.6 ± 5.5	0.647
Predicted Brain Age, mean ± SD years	67.8 ± 10.6	69.4 ± 8.6	0.592
Sex, no. (%)			0.076*
Male	6 (52.6)	6 (18.2)	
Female	8 (47.4)	27 (81.8)	
Race, no. (%)			0.304*
Caucasian	13 (92.9)	30 (90.9)	
African American	0 (0)	2 (6.1)	
Asian/Pacific Islander	1 (7.1)	0 (0)	
Other	0 (0)	1 (3.0)	
Education, no. (%)			0.133*
High school	2 (14.3)	11 (33.3)	
Two-year	1 (7.1)	7 (21.2)	
Four-year	2 (14.3)	7 (21.2)	
Masters	7 (50.0)	6 (18.2)	

Doctorate	2 (14.3)	2 (6.1)	
CES-D, mean ± SD years	5.9 ± 5.0	8.8 ± 5.4	0.085*
3MS, mean ± SD years	99.1 ± 1.3	97.3 ± 3.4	**0.008***
Duration of Pain, mean ± SD years	-	6.3 ± 8.8	-
Worst Pain Intensity	-	5.2 ± 1.9	-
# of Anatomical Pain Sites	-	3.1 ± 2.2	-
Medications, no. (%)	5 (38.5)	16 (48.5)	0.421*
Narcotic Medications (PRN), no. (%)	0 (0)	6 (18.2)	0.088*
Antidepressant Medications, no. (%)	1 (7.1)	9 (27.3)	0.123*
Anticonvulsant Medications, no. (%)	0 (0)	4 (12.1)	0.173*
NSAID Medications, no. (%)	4 (28.6)	16 (48.5)	0.207*

*X^2

Table 2. Self-reported health and lifestyle characteristics between the groups.

"*Have you ever had…*"	**No Chronic Pain (n=14)**	**Chronic Pain (n=33)**	**p-value**
High Blood Pressure, no. (%)	5 (35.7)	15 (45.5)	0.537*
Diabetes, no. (%)	1 (7.1)	3 (9.0)	0.827*
Anemia, no. (%)	5 (38.5)	12 (36.4)	0.966
Heart Trouble, no. (%)	2 (14.3)	3 (9.0)	0.597
Asthma, no. (%)	3 (21.4)	2 (6.1)	0.118
Bronchitis, no. (%)	6 (52.6)	16 (48.5)	0.724
Allergies, no. (%)	7 (50.0)	16 (48.5)	0.775
Cancer, no. (%)	6 (52.6)	13 (39.4)	0.825
Lung Disease, no. (%)	1 (7.1)	0 (0)	0.121
Kidney Trouble, no. (%)	3 (21.4)	3 (9.0)	0.246
Liver Trouble, no. (%)	1 (7.1)	2 (6.1)	0.890
Mononucleosis, no. (%)	3 (21.4)	6 (18.2)	0.796
Measles, no. (%)	13 (92.9)	28 (84.8)	0.452
Migraine, no. (%)	1 (7.1)	5 (15.2)	0.452
Skin Disease, no. (%)	4 (28.6)	7 (21.2)	0.586
Thyroid Problems, no. (%)	3 (21.4)	7 (21.2)	0.987

Ulcer, no. (%)	4 (28.6)	14 (42.4)	0.472
Do you exercise regularly, no. (%)	**14 (100)**	**23 (69.7)**	**0.020***
Do you smoke, no. (%)	1 (7.1)	2 (6.0)	0.890*
Do you drink alcoholic drinks, no. (%)	10 (71.4)	17 (51.5)	0.207*

Table 3. Distribution of anatomical pain locations in our participants (n=33).

	N (%)*
Head	1 (3.0)
Arms	5 (15.2)
Hand	11 (33.3)
Neck	10 (30.3)
Shoulders	11 (33.3)
Chest	2 (6.1)
Stomach	2 (6.1)
Pelvis	3 (9.1)
Upper Back	7 (21.2)
Lower Back	13 (39.4)
Knees	12 (36.4)
Legs	4 (12.1)
Feet	4 (12.1)

*Please note that % will not add to 100% given than most individuals experienced more than one pain simultaneously.

FIGURE LEGENDS

Figure 1. Study methods. A) Data used in the study comprising the 'brain-age' training sample of n=2646 healthy individuals and the current experiment cohort (n=47) comprising those with chronic pain (n=33) and those without (n=14). B) Image pre-processing, applied to all images, used SPM12 software to segment T1-weighted MRIs into gray and white matter probability maps. These were then spatially-normalized using DARTEL non-linear registration to a custom template in MNI152 space, with $1.5mm^3$ voxels, using 4mm spatial smoothing. These normalized 3D images were converted into 1D vectors and the gray and white matter vectors concatenated. C) Machine learning age prediction involved generating a linear kernel by calculating the dot-product of all pairs of image vectors across all participants, resulting in a similarity matrix. The similarity matrix was used as input into a Gaussian Processes regression to predict chronological from the image vectors. The model trained on the full training set was then applied to the n=47 participants from the chronic pain study to generate a brain-predicted age value for each participant. D) Statistical analysis was conducted to evaluate performance of the regression model performance using ten-fold cross-validation. Brain-predicted age difference (brain-PAD) was then calculated for the chronic pain study participants; whereby chronological age was subtracted from brain-predicted age. Brain-PAD was then used for subsequent statistical analysis of pain-related variables.

Figure 2. Location of worst pain reported by our sample (n=33).

Figure 3. Predicted brain age difference (predicted brain age – chronological age) across the groups (n=47) adjusted for chronological age, sex and exercise.

Figure 4. Brain-PAD in pain participants who reported having any treatments or trying any self-remedies (something they may have done at home) to relieve their worst pain during the past 3 months (n=19) compared to those that did not (n=14).

Figure 5. Associations between brain-PAD and percent relief reported from medication in our sample (n=16).

Figure 6. Associations between brain-PAD and psychological function in older individuals with chronic pain (n=33).

Figure 7. Associations between brain-PAD and somatosensory function in our sample (n=47).

Figure 8. Associations between brain-PAD and CPM in older individuals with chronic pain (n=33).

Figure 9. CPM in a subset of pain participants who had a younger appearing brain (n=16) compared to those that had an older appearing brain (n=11).

Submit figures separately as TIFF or EPS files in 300 dpi resolution (or greater). Do not embed them in a Word document.

FIGURES

Figure 1. Study methods.

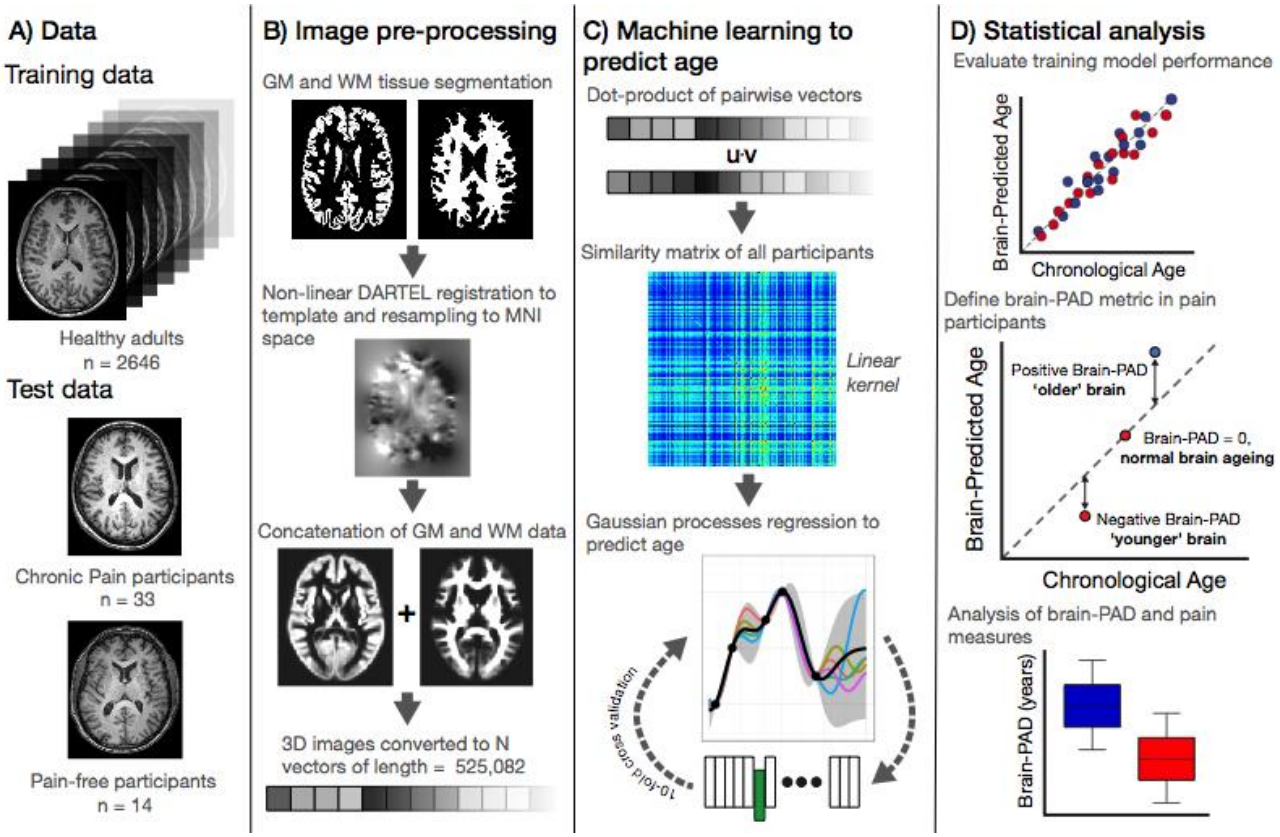

Figure 2. Location of worst pain reported by our sample (n=33).

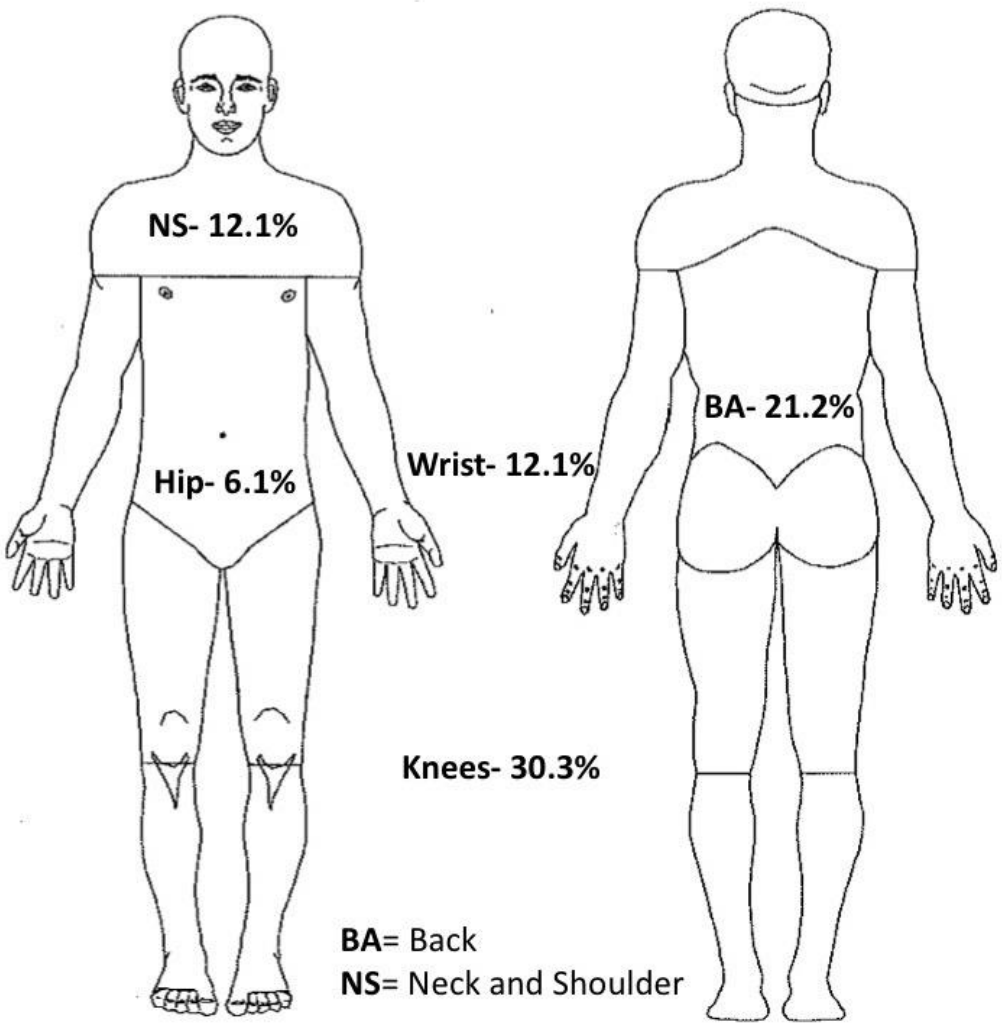

Figure 3. Adjusted predicted brain age difference (predicted brain age – chronological age) across the groups (n=47).

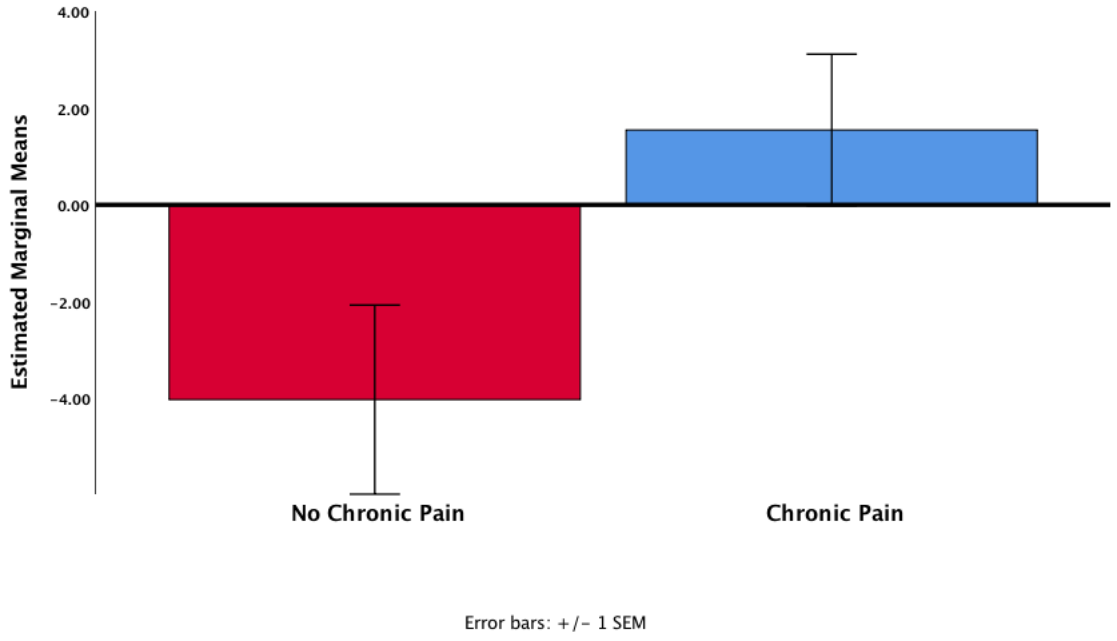

Figure 4. Brain-PAD in pain participants who reported having any treatments or trying any self-remedies (something they may have done at home) to relieve their worst pain during the past 3 months (n=19) compared to those that did not (n=14).

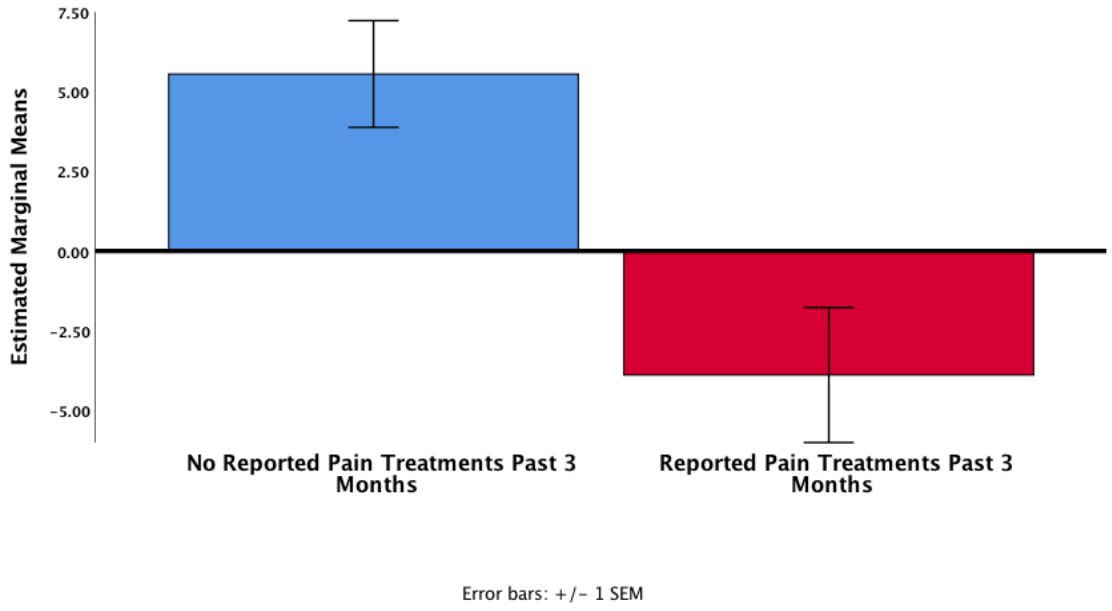

Figure 5. Associations between brain-PAD and percent relief reported from medication in our sample (n=16).

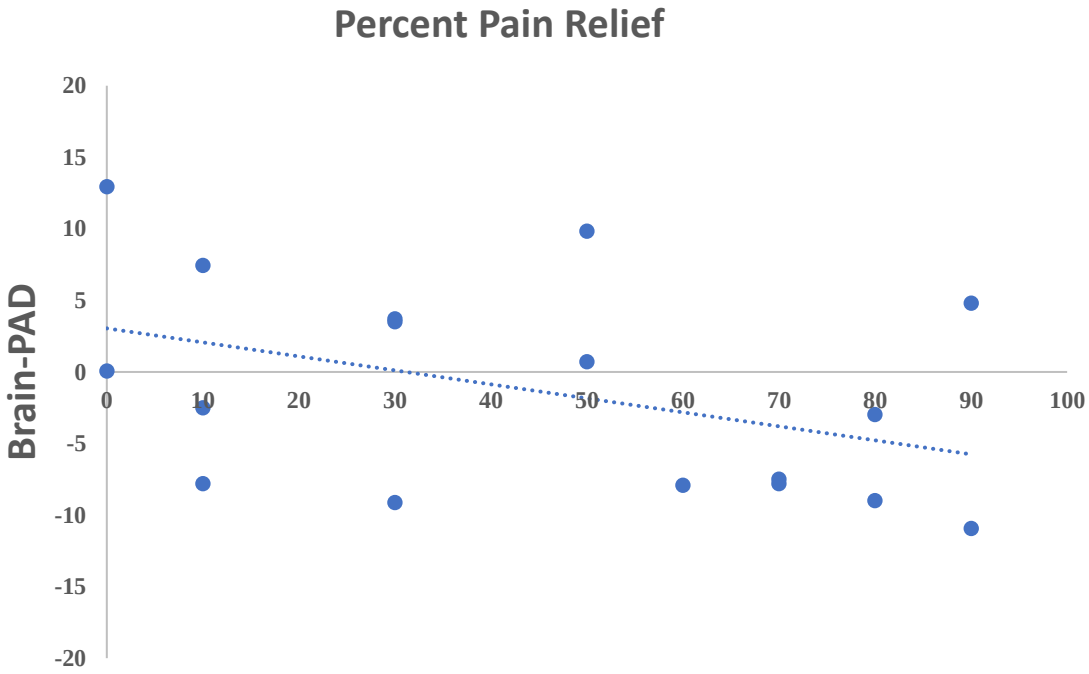

Figure 6. Associations between brain-PAD and psychological function in older individuals with chronic pain (n=33).

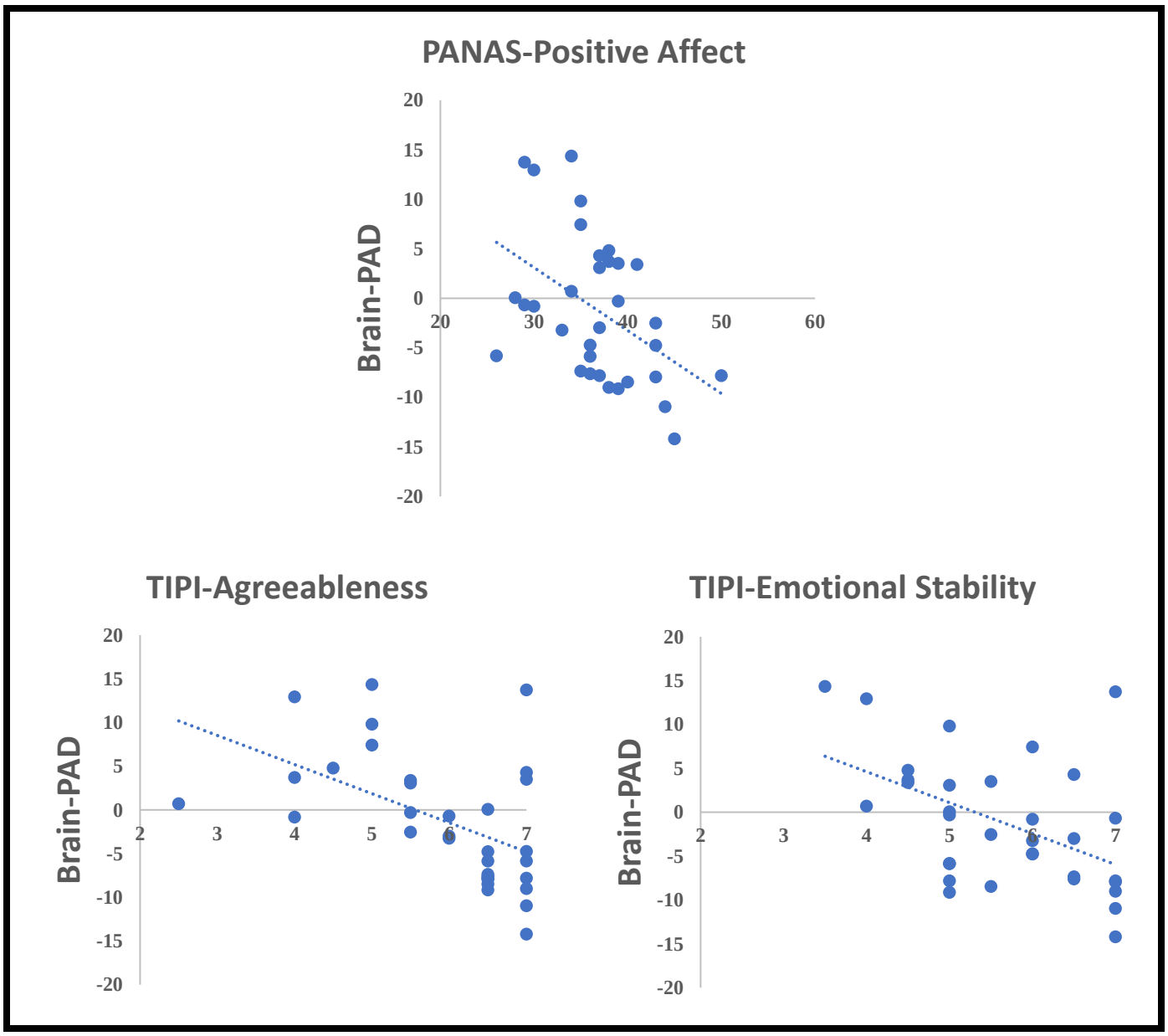

Figure 7. Associations between brain-PAD and somatosensory function in our sample (n=47).

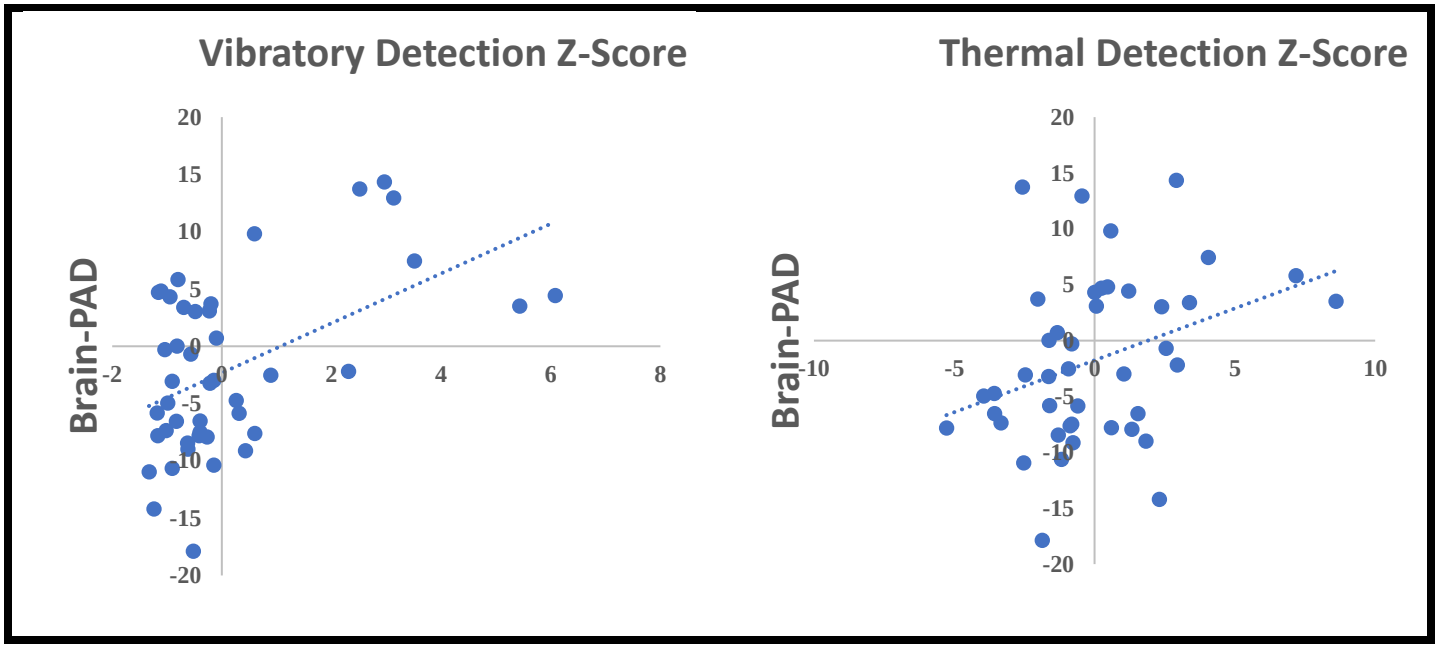

Figure 8. Associations between brain-PAD and CPM in older individuals with chronic pain (n=33).

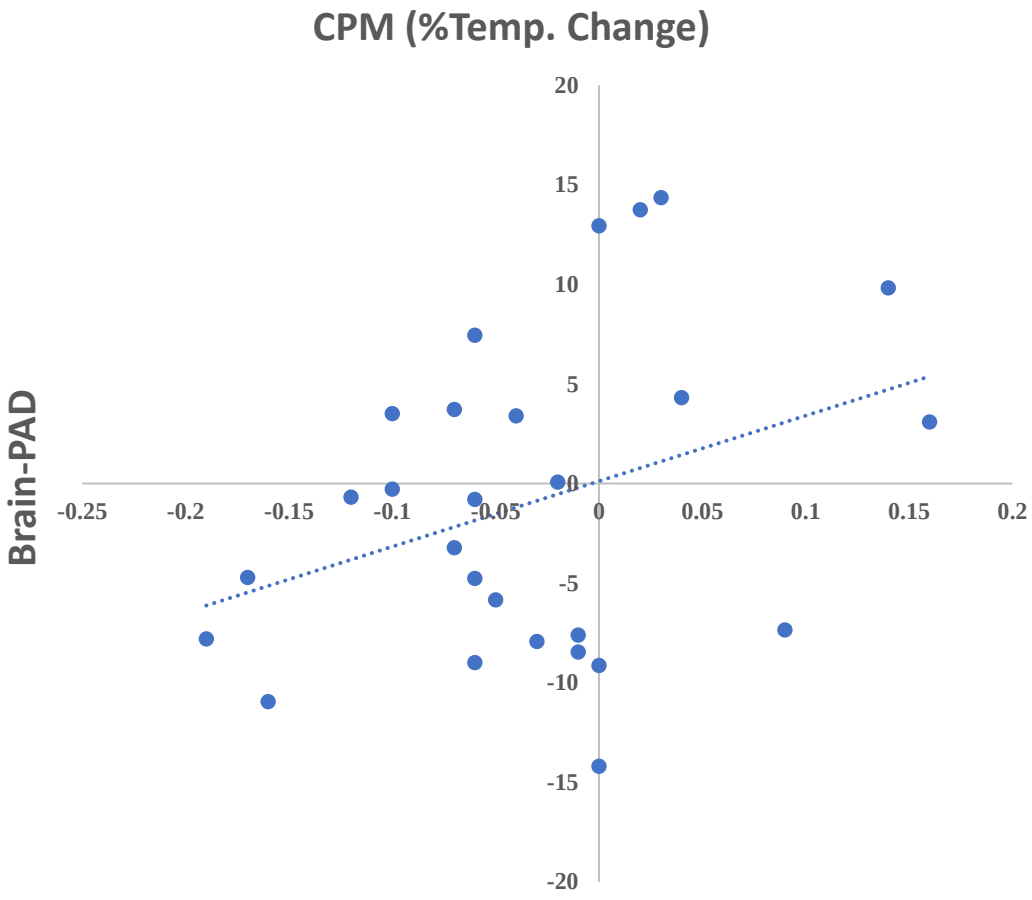

Figure 9. CPM in a subset of pain participants who had a younger appearing brain (n=16) compared to those that had an older appearing brain (n=11).